REMARKS

The Examiner noted that one of the inventors for the instant application was listed as "Monath P. Thomas," instead of "Thomas P. Monath." Accordingly, Applicants will provide a supplemental Declaration pursuant to 37 CFR 1.67 correctly setting forth the inventor's name as "Thomas P. Monath."

Paragraph 001 of the specification has been amended to correctly set forth the priority claim, and secure consistency between the specification, and the filing receipt and application transmittal (both of which correctly describe the application as a continuation in part of U.S. Application Serial No. 10/282,231).

New claims 16-25 have been added to more particularly and distinctly claim specific embodiments of the invention. Claims 7, 9, 12 and 14 have been cancelled without prejudice. Accordingly, after entry of this amendment claims 1-6, 8, 10, 11, 13, and 15-25 will be pending.

New claims 16-25 have been added to more particularly and distinctly claim specific embodiments of the invention. Specifically, new claim 16 has been added to specify a method for inducing an immune response to a flavivirus viral antigen in a subject, comprising delivering a chimeric yellow fever virus expressing an envelope gene product of a flavivirus to a subject's skin using a device comprising at least one microneedle. New claim 23 has been added to specify a kit for use in inducing an immune response to a flavivirus viral antigen in a subject, said kit comprising: (a) a chimeric yellow fever virus expressing an envelope gene product of a flavivirus and (b) a device comprising at least one microneedle.

The new claims are fully supported by the instant specification. In particular, support for a device comprising at least one microneedle as recited in new claims 16 and 23 can be found, for example, at ¶¶ 27, 47, 91, 109 and 110; in Example 6.2; and in claims 9 and 14 as originally filed. Support for new claims 17 and 18 can be found, for example, in claims 2 and 3 as originally filed. Support for claim 19 can be found, for example, at ¶ 20. Support for new claims 20 and 21 can be found, for example, at ¶¶ 29 and 32. Support for new claims 22 and 24 can be found, for example, at ¶ 91. Accordingly, no new matter has been added.

1. THE REJECTION UNDER 35 U.S.C. 112, 2nd PARAGRAPH SHOULD BE WITHDRAWN

Claims 1-7, 9-12, and 13-14 stand rejected under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which the applicants regard as their invention. Specifically, the Examiner contends that the recitation of "a device that abrades" is unclear as to what the term encompasses.

Without conceding the correctness of the rejection, Applicants have cancelled claims 7, 9, 12 and 14 without prejudice and have added new claims 16-25. New claims 16-25 specify a method and kit having a device comprising at least one microneedle. Moreover, Applicants refer the Examiner to the description of the term "abrade" as set forth in ¶ 81 of the instant specification. The term "abrade" refers to removing at least a portion of the stratum corneum to increase the permeability of the skin without causing excessive skin irritation or compromising the skin's barrier to infectious agents. The term "abrade" is used in contrast to "puncturing" which produces discrete holes through the stratum corneum with areas of undisrupted stratum corneum between the holes. Applicants respectfully submit that the term and the pending claims are definite. Accordingly, the Examiner's rejection is moot and should be withdrawn.

2. THE REJECTION UNDER 35 U.S.C. 112, 1st PARAGRAPH SHOULD BE WITHDRAWN

Claims 1 and 11 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims. The gravamen of the rejection is that *while the specification is enabling for Japanese Encepahilitis or Dengue virus* it does not reasonably provide enablement for other flaviviruses. Applicants respectfully disagree for the reasons detailed below.

First, the Examiner has relied on Chambers (U.S. Patent No. 6,696,281; "Chambers") as evidence that one of skill in the art could not necessarily construct a chimeric yellow fever virus expressing an envelope protein of other flaviviruses. The Examiner contends that Chambers indicates that there is "*some difficulty*" in generating constructs where the envelope protein of YF17D is replaced with a heterologous envelope protein from another flavivirus (*see*, Office Action, at p. 3). Applicants invite the Examiner's attention to the passage of Chambers at column 45, lines 13-42 that indicates the difficulties in preparing the plasmids to generate the chimeric viruses, and provides *the solution* to overcome the observed difficulties. Specifically, Chambers discloses a modification of the ChimeriVax procedure that replaces a two fragment ligation step with a three fragment ligation step to *successfully* obtain the desired plasmid. Moreover, the reference teaches that this modified approach can aid in resolving the difficulties in cloning genetic material from many flaviviruses (see, col. 46, lines 20-27). Accordingly, Chambers, itself, teaches a method to the skilled artisan to overcome the difficulties in preparing the desired constructs.

Moreover, Applicants respectfully points out that procedures for testing to see if a chimeric construct is capable of being recovered as an infectious replicative virus are routine in the art, and the skilled artisan would be able to determine without undue experimentation the successful engineering of such constructs. In fact, the Examiner erroneously conflates "difficulty" of experimentation with undue experimentation. However, "[t]ime and *difficulty* of experiments are *not* determinative if they are merely routine." *M.P.E.P. § 2164.06. (emphasis supplied).*

Furthermore, the test for enablement is whether one skilled in the art could make or use the invention without undue experimentation, from the disclosure in the patent specification coupled with the information known in the art at the time the application was filed. Under Section 112, it is not fatal that a certain amount of experimentation may be required to adapt the invention to a specific purpose, provided the experimentation is routine. In re Wands, 858 F.2d 731, 8 U.S.P.Q.2d 1400 (Fed. Cir. 1988). Moreover, a considerable amount of experimentation is permitted if it is merely routine or the specification provides a reasonable amount of guidance and direction to perform such experimentation. In re Jackson, 217 U.S.P.Q. 804, 807 (PTO Bd. Pt. App. Int. 1982).

Applicants submit that the instant specification coupled with the information which was readily available to the skilled artisan at the time the instant application was filed provides considerable direction and guidance on how to practice the claimed invention and enable the claims as currently pending (*see, e.g.*, 17-20). The specification provides guidelines on construction of recombinant chimeric flavivirus constructs for use in the methods of the invention. While these principles are exemplified using Japanese Encepahilitis or Dengue virus they are by no means limited to these viruses.

The provisions of Section 112, first paragraph, require that the description "enable *any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same* . . . (emphasis added). Applicants submit that any person skilled in the art of molecular biology can readily construct the chimeric viruses for use in vaccines as claimed by use of knowledge common in the art (*see, e.g.*, PCT Publication No. WO 01/39802, which is also incorporated by reference in its entirety in the instant application) and in view of the teachings of the present specification (*see, e.g.*, pages 17-20, teaching recombinant chimeric viruses encoded by viral vectors derived from genomes of Yellow Fever Virus and one or more other flaviviruses). The specification also provides ample disclosure to allow one of skill in the art to assay the claimed vaccines to ensure that they are viable and capable of eliciting an immune response. For example, the specification provides biochemical and/or immunochemical based assays, such as plaque assays to determine the growth rate of the chimeric constructs of the invention to assess their viability, in *in vitro* as well as *in vivo* systems (*see, e.g.*, the specification of the instant application at pages 30-33).

The specification provides the steps that the skilled artisan would take for the construction and use of a chimeric flavivirus construct comprising any member of the flavivirus family -- not simply Japanese Encephalitis or Dengue virus. The specification provides representative working examples of the successful construction of chimeric flaviviruses and their administration using multiple routes and devices. For example, ChimeriVax-JE (Example 6.2) was administered to an animal model, wherein the vaccine was administered either to the subcutaneous, intradermal or epidermal compartments of the skin. Blood samples were collected and viral replication and antibody mediated immune response were measured.

According to *M.P.E.P. § 2164.02*, "[f]or a claimed genus, representative examples together with a statement applicable to the genus as a whole will ordinarily be sufficient if one skilled in the art (in view of level of skill, state of the art and the information in the specification) would expect the claimed genus could be used in that manner without undue experimentation." In the instant case, in view of the level of skill, state of the art, and the information in the specification, one skilled in the art would recognize and appreciate that the teachings of the specification as exemplified for Japanese Encephalitis and Dengue virus are equally applicable to other members of the flavivirus family, given the similarity in genomic and structural organization and would not require undue experimentation.

The state of the art of molecular and viral biology at the time the application was filed was fairly advanced. The genomic organizations, sequences and biology of flaviviruses were well established and studied extensively, biochemically and immunologically. Analysis of chimeric viruses was routinely done using assays that were a standard practice in the art at the time the application was filed, *e.g.*, methods for measuring induction of immune response, plaques assays, replication based assays, ELISA, etc.

Additionally, there was a high level of skill in the art of viral molecular biology and immunology at the time when the application was filed. All the methods needed to practice the claimed invention including vaccine delivery and determining viral efficacy and viability were well known and routine in the art. Thus, the skilled artisan would have been able at the time of filing of the application generate the chimeric viruses of the invention, wherein the heterologous flavivirus was any flavivirus known in the art.

In fact, the instant specification provides an enabling methodology for construction of recombinant chimeric flavivirus constructs comprising a Yellow Fever Virus expressing a heterologous envelope protein gene product of another flavivirus. This is evidenced by post-filing publications: Arroyo (Arroyo et al., 2004, J. Virol. 78(22): 12497-12507; "Arroyo"), and Pugachev (Pugachev et al., 2004, Am. J. Trop. Med. Hyg. 71(5): 639-45; "Pugachev"), a copy of each is provided herein as Exhibits A and B respectively, and cited in the accompanying Supplemental Information Disclosure Statement. In Arroyo and Pugachev, the methodology set forth in the specification has been successfully applied for the construction of chimeric yellow fever virus expressing an envelope gene product from another virus. In Arroyo, a chimeric construct was produced wherein the envelope gene of the Yellow Fever Virus, strain 17D was replaced with the corresponding gene of the wild type West Nile virus (NY99 strain). In Pugachev, the envelope gene of Yellow Fever Virus, strain 17D was replaced with the St. Louis Encepahilitis virus. As demonstrated by the submitted post-filing publications, there is no evidence to support the Examiner's contention that the applicability of the claimed invention does not extend to other flaviviruses, beyond Japanese Encepahilitis or Dengue virus. In fact, the methods taught in the specification have been used to successfully construct chimeric constructs comprising other members of the flavivirus family.

Applicants respectfully maintain that the claims are enabled by the present specification, and request that the Examiner withdraw the rejection of claims 1 and 11 on this basis.

3. THE CLAIMED INVENTION IS NOT ANTICIPATED BY U.S. Patent No. 6,696,281 ("the '281 patent")

Claims 1, 3-6, 10-11 and 15 stand rejected under 35 U.S.C. § 102(e) as anticipated by U.S. Patent No. 6,696,281 ("the '281 patent"). The Examiner contends that the '281 patent discloses chimeric flavivirus vaccines having YF as the back bone into which the gene for the prM-E protein of another flavivirus is inserted. Furthermore, the Examiner notes that the '281 patent discloses a tetravalent vaccine for dengue infection that can be administered by "intramuscular, subcutaneous and intradermal routes." The Examiner asserts that the reference therefore contemplates the delivery of the vaccine to the epidermis of a subject. The Examiner suggests that the vaccine could be delivered to the epidermal compartment by a traditional syringe and needle. The entry of a needle, according to the Examiner, would displace the overlying skin and could form a kind of abrasion. Moreover, the Examiner posits that other devices (e.g., PowderJect) that would cause a form of abrasion would also work to deliver the vaccine.

Applicants respectfully disagree. The claimed invention, as specified in claims 1-15, relates to a method and kit that delivers a chimeric yellow fever virus expressing an envelope gene protein product of a flavivirus to a subject's skin using a device that abrades an epidermal layer of the skin's surface while delivering the chimeric virus. In order for a reference to anticipate a claim, it must teach every element of the claim. *M.P.E.P. § 2131.* Applicants respectfully submit that the '281 patent fails to teach or suggest the use of a device that abrades an epidermal layer of the skin's surface as required by the claimed invention. The term "abrade" refers to removing at least a portion of the stratum corneum to increase the permeability of the skin without causing excessive skin irritation or compromising the skin's barrier to infectious agents. The term "abrade" is used in contrast to "puncturing" which produces discrete holes through the stratum corneum with areas of undisrupted stratum corneum between the holes (*see* ¶ 81 of the instant specification).[1]

Similarly, the '281 patent fails to anticipate new claims 16-25. The claimed invention, as specified in claims 16-25, relates to a method and kit for inducing an immune response to a flavivirus viral antigen in a subject, comprising delivering a chimeric yellow fever virus expressing an envelope gene product of a flavivirus virus to a subject's skin using a device comprising at least one microneedle. Among other things, the microneedle in the claimed kit allows accurate targeting of the intradermal space and may allow for smaller doses of the chimeric flavivirus formulation to be administered via the intradermal route. *See*, for example, ¶ 90 of the instant specification. The '281 patent fails to teach or suggest the use of a microneedle for the delivery of a vaccine to a subject. In fact, as the Examiner concedes, the reference fails to explicitly disclose a device for delivery to the epidermal compartment.

Accordingly, absent a teaching of a device that abrades or a device that comprises at least one microneedle, the '281 patent fails to anticipate claims 1-25. Reconsideration and withdrawal of the rejection are respectfully requested.

4. THE CLAIMED INVENTION IS NOT ANTICIPATED BY Guirakhoo et al. J. Virol. 74(12) pp. 5477-5485.

Claims 11 and 15 stand rejected under 35 U.S.C. § 102(b) as anticipated by Guirakhoo et al. J. Virol. 74(12) pp. 5477-5485 ("Guirakhoo et al."). The Examiner asserts that Guirakhoo et al. teaches compositions for inducing an immune response to a flavivirus antigen in a subject, comprising delivering a chimeric YF virus expressing the envelope gene product of a flavivirus. The Examiner alleges that displacement of the overlying skin caused by entry of a needle could be a form of abrasion. The Examiner notes that claims 11 and 15 are silent with respect to the compartment into which the vaccine is delivered. Accordingly, the Examiner concludes that Guirakhoo et al. anticipates claims 11 and 15.

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[1] Moreover, Applicants respectfully submit that the Examiner's suggestions for delivering a vaccine to the epidermis of a subject, with a needle or with a Powderject device, combined with the disclosure of the '281 patent also fail to anticipate the invention as claimed.

Applicants respectfully disagree. In order for a reference to anticipate a claim, it must teach every element of the claim. *M.P.E.P. § 2131*. The claimed invention relates to a kit for use in inducing an immune response to a flavirus viral antigen in a subject. The claimed kit has a chimeric yellow fever virus expressing an envelope gene protein product of a flavivirus. The claimed kit also has a device that abrades an epidermal layer of the skin's surface while delivering the chimeric virus. The claimed kit, *inter alia*, is particularly useful for intradermal and epidermal delivery of the chimeric virus. Guirakhoo et al. fails to teach or suggest the use of a device that abrades an epidermal layer of the skin's surface. As noted, *supra*, the term "abrade" is used in contrast to "puncturing" which produces discrete holes through the stratum corneum with areas of undisrupted stratum corneum between the holes (*see* ¶ 81 of the instant specification). Consequently, the entry of a needle is not a form of abrasion as the Examiner contends.

Similarly, Guirakhoo et al. fails to anticipate new claims 23 and 25. The claimed kit has a chimeric yellow fever virus expressing an envelope gene protein product of a flavivirus. The claimed kit also has a device that comprises at least one microneedle. The cited reference fails to teach or suggest the use of a device that comprises at least one microneedle. Among other things, the microneedle in the claimed kit allows accurate targeting of the intradermal space and may allow for smaller doses of the chimeric flavivirus formulation to be administered via the intradermal route.

Accordingly, absent a teaching of the kits containing the devices as specified in claims 11, 15, 23 and 25, the rejection cannot stand. Applicants respectfully request reconsideration and withdrawal of the rejection.

THE CLAIMED INVENTION IS NOT RENDERED OBVIOUS BY Guirakhoo et al. IN VIEW OF Wu et al. (Nature Medicine 6(7) pp. 816-820).

Claims 1 and 3-15 stand rejected under 35 U.S.C. § 103(a) as being unpatentable over Guirakhoo et al. in view of Wu et al. (Nature Medicine 6(7) pp. 816-820). In particular, the Examiner asserts that Guirakhoo et al. discloses a method for inducing an immune response to a flavivirus viral antigen in a subject that includes delivering a chimeric yellow fever virus expressing an envelope gene product of a flavivirus virus. The reference, according to the Examiner, teaches that monkeys receiving the YF vaccine were protected against a challenge of wild-type dengue virus. Monkeys receiving only YF17K or no vaccine were unprotected.

The Examiner concedes, however, that Guirakhoo et al. fails to disclose delivering the vaccine to a subject's skin using a device that abrades an epidermal layer of the skin's surface while delivering the chimeric virus.

The Examiner relies on Wu et al. for the teaching that human skin Langerhans cells are targets of dengue virus infection. Specifically, the Examiner notes that the reference discloses a study that includes exposure of dendritic cells to dengue virus *ex vivo*. The Examiner asserts that Wu et al. concludes that dendritic cells are permissive for dengue virus infection, and suggests a possible mechanism for the transmission of the virus into human skin.

The Examiner concludes that one of ordinary skill in the art would have been motivated to administer the chimeric yellow fever virus because the skin is the route of entry and the target of many flaviviruses. Furthermore, the enhanced method of inducing the immune response using a chimeric yellow fever virus, according to the Examiner, would have been expected by one of ordinary skill in the art, based on the disclosure of Guirakhoo et al. Accordingly, the Examiner concludes that the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Applicants respectfully disagree with the Examiner's rejection as applied to claims 1 and 3-15, because the teachings of Guirakhoo et al. and Wu et al. fail to suggest the desirability of the proposed combination. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is a suggestion found in either the references themselves or in the knowledge generally available to one of ordinary skill in the art. *M.P.E.P. 2143.01*. Here, Wu et al. fails to suggest the desirability of administering flaviviruses to the epidermal space for the purpose of producing an immune response. Wu et al. describes a study conducted on cadaveric skin to demonstrate that dendritic cells are targeted when the virus contacts skin. However, when Wu et al. describes vaccinating a subject, the route of delivery is intramuscular, not epidermal. Therefore, Wu et al. teaches away from the claimed invention. Even assuming, *arguendo*, that Wu et al. provides a recognition that dendritic cell are permissive for the dengue virus infection, Wu et al. still administers the vaccine intramuscularly. Furthermore, while Guirakhoo et al. describes the benefits of subcutaneous administration of the vaccine, it fails to suggest the desirability of epidermal/intradermal delivery. Accordingly, absent a suggestion to combine the teachings of the references, the rejection cannot stand. Reconsideration and withdrawal of the rejection are respectfully requested.

Furthermore, Applicants submit that the invention as defined by the new claims 16-25 is also patentable in view of Guirakhoo et al. in combination with Wu et al. The new claims specify a method for inducing an immune response to a flavivirus viral antigen in a subject comprising delivering a chimeric yellow fever virus expressing an envelope gene product of a flavivirus virus to a subject's skin using a device comprising at least one microneedle. In addition, the new claims specify a kit for use in inducing an immune response to a flavivirus viral antigen in a subject. The kit has (a) a chimeric yellow fever virus expressing an envelope gene product of a flavivirus and (b) a device comprising at least one microneedle.

Applicants submit that the new claims are patentable because the cited references fail to teach use of a device that contains at least one microneedle. To establish a *prima facie* case of obviousness, the prior art references must teach or suggest all the claim limitations. *M.P.E.P. 2143.* Among other things, use of a microneedle allows accurate targeting of the intradermal space, and may allow for smaller doses of the chimeric flavivirus formulation to be administered via the intradermal route than by other routes of administration. Accordingly, reconsideration and withdrawal of the rejection are respectfully requested.

THE CLAIMED INVENTION IS NOT RENDERED OBVIOUS BY **Guirakhoo et al.** IN VIEW OF **Wu et al.** AND FURTHER IN VIEW OF MONATH ET AL. (**J. Virol. 74(4) pp 1742-1751**).

As a preliminary matter, the Office Action states that claim 2 stands rejected under 35 U.S.C. § 103(a) as being unpatentable over Guirakhoo et al. in view of Wu et al. as applied to claims 1 and 3-15 above, and further in view of Chambers et al. However, the Office Action describes the rejection citing to Monath et al. (J. Virol. 74(4) pp 1742-1755) and is silent with respect to the disclosure of Chambers et al. Accordingly, Applicants believe that the rejection is actually based on Monath et al., and therefore set forth their response based on this assumption.

The Examiner concedes that Guirakhoo et al. and Wu et al. fail to disclose Japanese encephalitis virus. The Examiner relies on Monath et al. for the disclosure of a yellow fever - Japanese encephalitis construct, and states that the immunized monkeys were protected from i.c. challenge from Japanese encephalitis challenge. The Examiner notes that Monath et al.

posits that virus injected by a mosquito that is sterilized by the host's antibody can boost the host's immunity. The Examiner concludes that the typical route of infection is by the skin, and that the delivery of the virus to the skin is sufficient to raise an antibody response.

The Examiner reasons that one of ordinary skill in the art would have been motivated to administer the chimeric yellow fever vaccine because the skin is said to be the route of entry and target of infection for many flaviviruses according to Wu et al. The Examiner contends that Monath et al. also implicates the i.d. route of delivery because it discloses that mosquito saliva containing virus boosts the immune response.

Applicants respectfully disagree with the Examiner's rejection, because the teachings of Guirakhoo et al., Wu et al. and Monath et al. fail to suggest the desirability of the proposed combination. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is a suggestion found in either the references themselves or in the knowledge generally available to one of ordinary skill in the art. *M.P.E.P. 2143.01.* Here, Wu et al. fails to suggest the desirability of administering flaviviruses to the epidermal space. As noted, *supra*, when Wu et al. describes delivering a vaccine to a human subject, the vaccine is delivered intramuscularly, and not to the epidermis. Even with the recognition that dendritic cells are permissive for the dengue virus infection, Wu et al. still administers the vaccine intramuscularly.

Monath et al. similarly fails to suggest to one of skill in the art the desirability of intradermal delivery of the chimeric vaccine. In fact, Monath et al. prominently highlights the immunogenicity of ChimeriVax-JE when it is administered subcutaneously. (col. 2, p. 1748). According to the reference, the test animals used in the study were "solidly protected against challenge by the wild-type JE." Skilled artisans, when viewing the disclosure of Monath et al. as a whole, would hardly conclude, as the Examiner alleges, that intradermal delivery of the chimeric vaccine would provide a superior innoculation method than the disclosed administration method. More likely, skilled artisans would conclude that subcutaneous administration of the ChimeriVax-JE would provide rapid immunity in mammals based on Monath et al.'s *in vivo* study.

Accordingly, absent a suggestion to combine the teachings of the references, the rejection cannot stand. Reconsideration and withdrawal of the rejection are respectfully requested.

CONCLUSION

In light of the above amendments and remarks, the Applicant respectfully requests that the Examiner enter the amendments and consider the remarks made herein. Withdrawal of all rejections, and an early allowance is earnestly sought. The Examiner is invited to call the undersigned attorney if a telephone call could help resolve any remaining items.

Respectfully submitted, by Jacqueline Benn
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